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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/679,258 | 10/07/2003 | Francesco Orlandi | 51637/76 | 3122 |

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KENYON & KENYON LLP
1500 K STREET N.W.
SUITE 700
WASHINGTON, DC 20005

EXAMINER

CLOW, LORI A

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| ART UNIT | PAPER NUMBER |
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1631

DATE MAILED: 09/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

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|------------------------------|--|---------------------------------------|--|
| Office Action Summary | Application No. 10/679,258 | Applicant(s) ORLANDI ET AL. | |
| | Examiner Lori A. Clow, Ph.D. | Art Unit 1631 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 June 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-38 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-38 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Applicants' arguments, filed 30 June 2006, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 1-38 are currently pending.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

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the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-38 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,573,103 B1(Wald), further in view of Stempfle et al. (Pediatric Radiology (1999) Vol. 29, pages 682-688), for the reasons set forth in the previous Office Action.

Response to Applicant's Arguments

Applicant argues the following:

"Applicant traverse this rejection at least because there is no reasonable expectation of success in using the BPD/OFD measurement, as described by Stempfle, as a marker for fetal abnormalities, in accordance with the methods of Wald.

Specifically, as shown in the articles attached as Exhibits A-C, previous studies that analyzed the BPD/OFD ratio (also referred to as the "cephalic index") determined that it was not an effective marker for Down's Syndrome. For example, Lockwood et al. (Exhibit A) examined a group of ultrasound markers and concluded that there were no statistically significant differences in the BPD/OFD ratio ("cephalic index") between control fetuses and Down's Syndrome fetuses between 15 and 23 weeks gestation (see Lockwood et al, Am J. Obstet Gynecol, 157:803-808, 805, 807 (1987)). As noted by Lockwood et al, these results were consistent with another study evaluating BPD/OFD ratio ("Perry et al, however, were not able to differentiate normal from Down syndrome fetuses on the basis of an increased cephalic index during second-trimester sonography. Our data confirm their observation, with no difference in cephalic index noted between case and control populations." (page 807)).

Similar results were obtained by Borrell et al. (Exhibit B), who evaluated fetuses at 13-18 weeks gestation and found that the comparison between control fetuses and Down syndrome fetuses did not show a significant difference in cephalic index² (see

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Borrell et al., "Brachycephaly is ineffective for detection of Down syndrome in early midtrimester fetuses," Early Human Dev. 47:57-61,60 (1996)).

Similar results were also obtained by Rosati and Guarglia (Exhibit C), who evaluated fetuses between 9 and 16 weeks gestation and concluded that early in pregnancy the cephalic index³ cannot be considered a useful tool in the detection of fetuses at risk for Down syndrome (see Rosati and Guariglia, "Early Transvaginal Measurement of Cephalic Index for the Detection of Down Syndrome Fetuses," Fetal Diag. Therapy, 14:38-40, 38 (1999)).

Therefore, based on the knowledge available prior to the filing date of the present application, one skilled in the art would not have had a reasonable expectation that the BPD/OFD ratio would be an effective marker for Down's Syndrome".

This is not persuasive. As set forth previously, it would have been prima facie obvious to one of ordinary skill in the art at the time of invention to use the ultrasound marker of BPD/OFD ratio of Stempfle et al. in the methods taught by Wald, as the primary marker. Wald motivates one to utilize such a marker at column 5, line 5, where he lists a series of ultrasound imaging markers and states that "measurements carried out on ultrasound images may include one or more of the following ultrasound markers of Down's syndrome, among others.

Applicant argues that "Stempfle does not provide a reasonable expectation that the BPD/OFD ratio would be a successful marker of Down's Syndrome during the first trimester of pregnancy".

This is not persuasive. Stempfle, at page 686, column 2, specifically teaches that there is a statistical difference in the BPD/OFD ratio between normal fetuses and those with trisomy 21 at all gestational ages. Stempfle specifically teaches that "the mean value of BPD/OFD ratio was statistically higher in trisomy 21 compared to the control group, whatever the GA (gestational

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age)”. Therefore, Stempfle’s statistical analysis is able to successfully differentiate between Down’s and normal ratios. Further, the combination of Wald in view of Stempfle, would have a reasonable expectation of success to obviate the instantly claimed method which is drawn to the assessment of fetal abnormality using the combination of the BPD/OFD ratio AND a secondary marker. In fact, Stempfle teaches that the ratio should be combined with other markers/measurements for higher accuracy, thus also providing a motivation to combine Wald and Stempfle (see page 686).

All claims remain rejected.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

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Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The Central Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (571) 272-0715. The examiner can normally be reached on Monday-Friday from 10 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

September 18, 2006
Lori A. Clow, Ph.D.
Art Unit 1631

Lori A. Clow

MARJORIE A. MORAN
PRIMARY EXAMINER

Marjorie A. Moran
9/18/06